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| 09/922,549 | 08/03/2001 | Jeffrey C. Rapp | AVI 013N | 1388 |

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| EXAMINER | |
|---|---|
| MCGILLEM, LAURA L | |
| **ART UNIT** | **PAPER NUMBER** |
| 1636 | |

DATE MAILED: 07/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/922,549 | RAPP, JEFFREY C. | |
| | Examiner | Art Unit | |
| | Laura McGillem | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *70,72-82,88-96, 102,104,105,107-115,121-136,138,139,141-174* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *88-96,121-128,134 and 135* is/are allowed.

6)☒ Claim(s) *70, 72-82, 102, 104, 105, 107-115, 136, 138, 139, 141-147 and 156-174* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.



5-00

## *DETAILED ACTION*

### *Priority*

The application claims priority to provisional application 60/280,004 filed 03/30/2001. Receipt of a Reply to Office action filed 11/3/2004 is acknowledged. Claims 71, 83 to 87, 97 to 101, 103, 106, 116 to 120, 137 and 140 have been canceled without prejudice to subsequent revival. Claims 156 to 175 have been added. Claims 70, 72-82, 88-96, 102, 104-105, 107-115, 121-136,138-139, 141-174 are pending.

### *Specification*

The use of the trademarks EFFECTENE, UNIFECTIN, MAXIFECTIN, LIPOFECTAMINE, LIPOFECTIN and SUPERFECT has been noted on page 29 in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 129-133 and 174 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **These are new rejections necessitated by Applicant's amendment of the claims in the response filed 5/13/2005.**

Claim 129-133 recites the limitation "the cell is". There is insufficient antecedent basis for this limitation in the claim. These claims are drawn to the expression vector of claim 121 wherein the cell is an avian, chicken, cultured, oviduct or tubular gland cell. Claim 121 has been amended to remove any language that refers to a cell, therefore the phrase "the cell" in claims 129-133 is unclear.

Claim 174 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 174 is drawn to the cell of claim 174. A claim cannot be dependent on itself. For the purposes of examination, claim 174 will be interpreted to mean "the cell of claim 173."

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

**The following are new rejections necessitated by the amendment filed on 11/03/2004.**

Claims 70, 72, 74-82, 102, 104, 107-115, 136, 138, 141-147, 156-165, 168-169, 172 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants claim an isolated DNA molecule comprising a gene expression controlling region comprising a nucleotide sequence at least 95% or 99% identical to SEQ ID NO:67, or 95% or 99 % identical to the complement of SEQ ID NO:67. Applicants also claim a fragment of a nucleotide sequence at least 95% identical to SEQ ID NO:67 wherein the fragment is functional as a gene expression controlling region, operably linked to a nucleotide sequence encoding a protein of pharmaceutical interest. The claimed invention also comprises expression vectors comprising said sequences and isolated cells comprising said sequences.

The written description requirement for a genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that applicant was in possession of the claimed

invention. In the instant case, the specification and prior art disclose one nucleotide sequence of a gene expression controlling region comprising a nucleotide sequence of. There is no description of which mutational sites which might naturally occur in the SEQ ID NO:67 and there is no description of how the structure of the disclosed SEQ ID NO:67 relates to the structure of a nucleotide sequence which is 95% or 99% identical to SEQ ID NO:67 or 95% or 99 % identical to the complement of SEQ ID NO:67 and to the function of these molecules as gene expression controlling regions. The genus would be expected to have divergent functional properties as small changes in the sequence can have significant effects on the structure and properties of a nucleotide sequence. Neither applicant nor the prior art provides an indication of how the structure of SEQ ID NO:67 is representative of nucleotide sequences that are 95% or 99% identical to SEQ ID NO:67 or 95% or 99 % identical to the complement of SEQ ID NO:67 having gene expression controlling functions. The common attributes of the genus are not described and the identifying attributes of nucleotide sequences that are 95% or 99% identical to SEQ ID NO:67 or 95% or 99 % identical to the complement of SEQ ID NO:67 (other than the disclosed sequence) are not described. According to these facts, one of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only one member of this genus is not representative of the variants of the genus and is insufficient to support them.

Claims 70, 72-82, 102, 104, 105, 107-115, 136, 138, 139, 141-147 and 156-174 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while

being enabling for a nucleotide sequence identical to SEQ ID NO:67, does not reasonably provide enablement for a nucleotide sequence at least 95% or 99% identical to SEQ ID NO:67, or 95% or 99% identical to the complement of SEQ ID NO:67. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Applicants claim an isolated DNA molecule comprising a gene expression controlling region comprising a nucleotide sequence at least 95% or 99 % identical or identical to SEQ ID NO:67, or 95% or 99 % identical or identical to the complement of SEQ ID NO:67. Applicants also claim a fragment of a nucleotide sequence at least 95% identical to SEQ ID NO:67 wherein the fragment is functional as a gene expression controlling region, operably linked to a nucleotide sequence encoding a protein of pharmaceutical interest. The isolated nucleotide sequence can comprise a 5' matrix attachment region, an intrinsically curved region of DNA, a transcription enhancer, a negative regulatory element, at least one hormone responsive element, and avian CRI repeat element, a proximal lysozyme promoter or signal peptide encoding region, or a polyadenylation signal sequence wherein the signal sequence is derived from the SV40 virus. The claimed invention also comprises expression vectors comprising said sequences and isolated cells comprising said sequences.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with the information known in the art without undue experimentation (*United States v. Teletronics Inc.*, 8

USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors (See *Ex parte* Forman, 230 USPQ 546 (Bd. Pat App.& Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). These factors include the following:

**1) Unpredictability of the art.** The ability to make or use the instant invention is unpredictable, based on the large number of sequences that are encompassed by the limitations of this claim which are required to be gene expression controlling regions. Table II of the instant specification lists fragments of the complete lysozyme promoter sequence (SEQ ID NO:67) which are homologous to known promoter sequences. Sequence identity between each of these functional fragments and SEQ ID NO:67 ranges from 87%-100% as listed in Table II. Although some variations of the nucleotide sequence in the range from 87%-100% in these individual fragments may allow the nucleotide sequence to retain functionality, there is no evidence to predict that variations of at least 95% or 99% of the entire nucleotide sequence of SEQ ID NO:67 would retain a structure that would allow function as a gene expression controlling region. SEQ ID NO:67 and its complement are 12758 nucleotides in length, and 95% of 12758 nucleotides is ~12120 nucleotides leaving a possibility of variation of ~637 nucleotides. In claim 72, 99% of the length of SEQ ID NO:67 and its complement is ~12120 nucleotides leaving a possibility of variation of ~127 nucleotides. Therefore, an immense number of variations to a nucleotide sequence at least 95% or 99% identical to SEQ ID NO:67 or 95% or 99% identical to the complement of SEQ ID NO:67 are required to function as a gene expression controlling region. The specification has

provided no guidance on what sequences 95% or 99% identical to SEQ ID NO:67 or its complement would have functional activity as a gene expression controlling region.

The ability to use a nucleic acid sequence that is a complement of SEQ ID NO:67 or at least 95% or 99% identical to a complement of SEQ ID NO:67 for a gene expression controlling region is also unpredictable. The unpredictability is manifested in the ability of a nucleotide sequence that is complementary to a nucleotide sequence with a function, such as control of gene expression to have that same function. With regard to complementary nucleotide sequences, Alberts et al (1994. Molecular Biology of the Cell 3rd ed. Garland Publishing, New York) defines a complementary nucleotide sequence as a sequence of nucleotides that pairs with a template of another nucleotide sequence (See Alberts et al, page 6, Figure 1-4 and 1-5, for example). It would be obvious to the skilled artisan that the complementary sequence of a first nucleotide sequence would be composed of matching nucleic acid base pairs. In transcription of DNA to RNA, only one strand of nucleic acids is used as the template to make RNA which will eventually code for a polypeptide (See Alberts et al, page 227, Figure 6-6 and paragraph 1, for example). The complement of the template nucleic acid sequence, although made up of nucleic acids which pair with the first nucleic acid sequence, will not code for that same polypeptide. Although SEQ ID NO:67 does not code for a polypeptide, SEQ ID NO:67 does have a function as a gene expression controlling region.

**2) State of the art** There is no prior art which is predictive of the function of nucleotide sequences that are at least 95 or 99% identical to SEQ ID NO:67 or its

complement as gene expression controlling regions. Given that the applicant provides no data which is art recognized as being predictive of gene expression controlling results by the complement of a gene expression controlling region, it must be considered that the skilled artisan would have had to have practiced trial and error experimentation in order to attempt to practice the claimed invention. The art at the time the invention was made does not teach the use of the complementary sequences of gene expression controlling regions to regulate gene expression.

**3) Amount of guidance presented by applicant**. There are no working examples provided in the specification which demonstrate gene expression control function by a DNA molecule structure comprised of nucleotide sequences which are at least 95% or 99% identical to SEQ ID NO:67 or 95% or 99% identical to its complement. The applicant presents no guidance on how to make or use a nucleotide sequence that is the complement of SEQ ID NO:67 as a gene expression controlling region.

**4) Number of working examples.** Applicant presents no working examples of gene expression control function by nucleotide sequences which are at least 95% or 99% identical to SEQ ID NO:67 or 95% or 99% identical to its complement.

**5) Scope of the claims.** Absent guidance of example of how to modify a nucleotide sequence that is at least 95% or 99% identical to SEQ ID NO:67 or its complement, there would be a extremely large number of possible variants of SEQ ID NO:67 which might be effective as gene expression controlling regions. The broadest interpretation of the claims drawn to a nucleotide sequence that is 95% or 99% identical to the complementary strand of SEQ ID NO:67 reads on an extraordinary number of

nucleotides that must function as a gene expression controlling region. Absent any information to how to make a nucleotide sequence that is 95% or 99% identical to the complement of SEQ ID NO:67 or is identical to the complement of SEQ ID NO:67 that would be effective in controlling gene expression, the claims encompass an immense number of sequences. The skilled artisan would have to conduct undue and excessive trial and error experimentation to vary the sequence and then determine if expression controlling activity is retained by that variant of SEQ ID NO:67.

**6) Nature of the invention.** The invention involves complex and unpredictable aspects of molecular biology, including the use of nucleic acid sequences and variants of nucleic acid sequences that are at least 95% identical, 99% identical or identical or complementary to a functional gene expression controlling region.

**7) Level of skill in the art.** The level of skill in the art is high; however given the unpredictability of the art, poorly developed state of the art and the lack of guidance presented by the applicants, the skilled artisan would have had to have practiced trial and error experimentation in order to attempt to practice the claimed invention.

Given the analysis of the above factors which the Court have determined are critical in determining whether a claimed invention is enabled, it must be considered that the skilled artisan would have needed to have practiced undue and excessive experimentation, with little guidance from applicant in order to attempt to practice the claimed invention.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 74-82 are rejected under 35 U.S.C. 102(b) as being anticipated by Wolfl et al (PNAS. 1991, 88:271-275). **These are new rejections necessitated by amendment.** Applicants claim an isolated DNA molecule comprising a fragment of a nucleotide sequence at least 95% identical to SEQ ID NO:67 wherein the fragment is functional as a gene expression controlling region operably linked to a nucleotide sequence encoding a protein of pharmaceutical interest. The isolated nucleotide sequence can comprise a 5' matrix attachment region, an intrinsically curved region of DNA, a transcription enhancer, a negative regulatory element, at least one hormone responsive element, and avian CRI repeat element, a proximal lysozyme promoter or signal peptide encoding region, or a polyadenylation signal sequence wherein the signal sequence is derived from the SV40 virus

Absent a clear definition in the specification of what constitutes a "protein of pharmaceutical interest", the claims will be broadly interpreted. The promoter region is operably linked to a chicken lysozyme gene, therefore it is inherently functional as a gene expression controlling region for a protein of pharmaceutical interest. In order to provide rationale and evidence to show that lysozyme is inherently a protein of

pharmaceutical interest, Examiner directs applicant to review Wagstrom et al (Viral Immunology 2000(13):383-7). Although this claim is rejected under 35 U.S.C. 102(b), it is permissible to present a second reference to substantiate an inherent property. Please see MPEP 2112, quoted as follows:

"The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill."

Wolfl et al teaches a portion of a chicken lysozyme gene and its upstream proximal promoter. The nucleotides 1-522 of a 720 bp nucleotide sequence disclosed by Wolfl et al displays 99.2% local identity with nucleotides 11424-11938 of SEQ ID NO:67 (See EMBL accession number J00886). Lysozyme is a protein of pharmaceutical interest because it is an enzyme with antimicrobial activity found in secretions, tissues and phagocytic cells of mammals as taught by Wagstrom et al (Viral Immunology 2000(13):383-7). Lysozyme is thought to have antibacterial functions, including activation of the immune system by interaction with complement (See Wagstrom et al, page 390, last paragraph, in particular). Therefore, the teachings of Wolfl et al read on

an isolated DNA molecule comprising a fragment of a nucleotide sequence at least 95% identical to SEQ ID NO:67 wherein the fragment is functional as a gene expression controlling region operably linked to a nucleotide sequence encoding a protein of pharmaceutical interest. Claims 76-79 and 81-82 are rejected as dependent on a rejected claim.

***Conclusion***

Rejections of claims in the previous office action which have not been mentioned herein are withdrawn. Claims 88-96, 121-134 and 148-155 are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura McGillem whose telephone number is (571) 272-8783. The examiner can normally be reached on M-F 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DAVID GUZO
PRIMARY EXAMINER

Laura McGillem, PhD
7/25/2005